REMARKS/ARGUMENTS

Claim 15 has been amended to correct a typographical error. Claims 15-23 are pending in the application. Applicants have also submitted with this response an unsigned declaration under 37 C.F.R. § 1.132 from an inventor of the application. A signed copy of the declaration will be submitted shortly. Entry of the Amendment and reconsideration of the claims in view of the following Remarks is respectfully requested.

35 U.S.C. 103

Claims 15-23 stand rejected under 35 U.S.C. 135 103(a) as unpatentable over *Huland* et al. in view of both *Debs* et al. and *Ruskewicz* et al. The Examiner contends that *Huland* et al. teach an aerosol composition comprising a stabilizing agent containing a salt, a sugar, an amino acid, an alcohol such as polyethylene glycol, or a combination. The Examiner further contends that *Huland* et al. teach the inclusion of cytokines in the aerosol composition including gamma-IFN. Applicants respectfully traverse this rejection.

Independent claims 15 and 22 each recite aerosol compositions having a gamma-IFN biological activity and "comprising a stabilizing agent consisting of sugar, alcohol, amino acid, or combination thereof." The claims also recite that the aerosol has a "g-IFN biological activity substantially the same as that of the solution." Applicants submit that *Huland* et al. do not teach an aerosol composition having these limitations. Rather, *Huland* et al. teach solutions that can comprise a variety of cytokines, one of which is gamma-IFN. The *Huland* et al. solutions comprise a serum protein, and preferably human serum albumin, as a stabilizing agent (column 5, lines 23-27). As stated in Applicants' previous Response, the purpose of the serum protein is to optimize the biological effect of the cytokine, and to lead to a better recovery after in vitro nebulization (lines 24-27). *Huland* et al. disclose that serum protein concentrations of between 0.1-20% by weight of the aerosol correlated in a dose-dependant manner with the level of recovery of the cytokine after nebulization (column 5, lines 35-37). Furthermore, *Huland* et al. teach that only at very high levels of cytokine (at least 0.5 mg/ml) can the serum protein be omitted while still allowing recovery and biological activity of the drug (column 5, lines 37-39). The Examiner has acknowledged that the foregoing characterization of *Huland* et al. is correct (page 3, first full paragraph of the Office Action).

In response, however, the Examiner now asserts that "the instant claims do not expressly

exclude serum albumin." (page 3 of the Office Action). Applicants respectfully submit, however, that the present claims do expressly recite that the stabilizing agent consists of a sugar, alcohol, amino acid, or combination thereof. The present claims expressly exclude the compositions disclosed by *Huland* et al. that use a serum protein, rather than a sugar, alcohol, amino acid, or combination thereof as the stabilizing agent.

The Examiner has pointed to portions of the *Huland* et al. reference to support the contention that the reference teaches that the aerosol composition may contain sugars, alcohols, and amino acids. Applicants submit, however, that these compounds as taught by *Huland* et al. are not used as stabilizing agents. As stated above, and as acknowledged by the Examiner, *Huland* et al. teach that the inclusion of a serum protein in the aerosol compositions is necessary to optimize the biological effect of the cytokine, and lead to a better recovery of the cytokine after nebulization. Indeed, as stated above, *Huland* et al. explicitly assert that the level of recovery of the cytokine after nebulization correlates in a dose-dependent manner with the serum protein concentration. Therefore, the aerosol compositions taught by *Huland* et al. depend on the presence of serum albumin as an agent to stabilize the cytokine aerosol.

The Examiner now asserts, however, that there is no teaching in *Huland* et al. that the biological activity of the cytokine in the aerosol composition is substantially different from that of solution. The Examiner states that absent evidence to the contrary, it is assumed that the cytokine activity of the aerosol compositions in *Huland* et al. is substantially the same as that of solution. Applicants respectfully disagree, and submit that the Examiner's argument is not consistent with the explicit language of the reference. As stated above and admitted by the Examiner, *Huland* et al. acknowledge that the addition of a serum protein "optimizes the biological effect of the cytokine," and that only at very high cytokine concentrations can human serum albumin be omitted and still allow recovery and biological activity of the cytokine. Applicant submits therefore, that the plain language of *Huland* et al. teaches that the biological activity of the cytokine in the aerosol composition is substantially different from that of solution, in the absence of a serum protein as a stabilizing agent.

It is the Applicants who have discovered that a sugar, alcohol, amino acid, or combination thereof can replace a serum protein as a stabilizing agent in an aerosol form, while maintaining gamma-IFN biological activity substantially the same as that of gamma-IFN in solution. Applicants submit that *Huland* et al. nowhere teach or suggest that the serum albumin stabilizing agent can be replaced with these compounds or a combination thereof, while still

maintaining the biological activity of gamma-IFN in an aerosol. There is no teaching or suggestion that the sugars, alcohols, or amino acids disclosed in *Huland* et al. can be stabilizing agents. *Huland* et al. teach that a sugar solution can serve as "an aqueous carrier solution" (column 5, lines 45-47). With respect to amino acids, *Huland* et al. teach that a variety of different types of compounds, including amino acids, can be an "additive" (column 5, lines 55-57). Similarly, *Huland* et al. teach that a list of compounds, including the alcohol polyethylene glycol, can be used as "detergents" (column 5, line 65 through column 6, line 3). *Huland* et al. nowhere teach or suggest that any of these compounds are stabilizing agents or can be stabilizing agents in gamma-IFN solutions. Indeed, the disclosure of *Huland* et al. that the absence of a serum protein in cytokine aerosol solutions that can comprise a sugar, alcohol, or amino acid results in a loss of recovery and biological activity teaches away from the use of these compounds as stabilizing agents.

The Examiner contends that Applicants' previous arguments regarding the effect of aerosolization on the stability of gamma-IFN relate to limitations not present in the instant claims. In response, Applicants submit that these adverse effects on stability were known in the art at the time of filing, and that the instant claims recite novel, nonobvious compositions for overcoming the effects. Applicants have submitted with this response a declaration by one of the present inventors asserting that it was known at the time of invention that shear forces and other physico-chemical challenges, such as those encountered during attempts to aerosolize a liquid gamma-IFN solution, are not well tolerated by the molecule. (Declaration, third paragraph). The Declaration also states that gamma-IFN was known to be active in a non-covalent dimeric form, but not in its monomeric form, and it was believed that aerosolization may lead to loss of activity by creating shear conditions that result in the conversion of gamma-IFN to the inactive monomeric form. *Id.* Therefore, at the time of invention, it was believed that a stabilizing agent was required in the gamma-IFN solution to generate an aerosol having a gamma-IFN activity substantially the same as that of gamma-IFN solution (Declaration, fourth paragraph). Previously, serum albumin protein was commonly used as a stabilizing agent. *Id.* The *Huland* et al. reference, accordingly, is understood to disclose only the use of a serum protein as a stabilizing agent. The use of serum protein, however, has disadvantages in that it can lead to infection. *Id.*

Applicants' claims recite compositions having only sugar, alcohol, amino acid, or a combination thereof as a stabilizing agent. *Huland* et al. do not appear to appreciate the use of

anything other than a serum protein as a stabilizing agent (Declaration, paragraph 6).

Furthermore, Applicants submit that neither *Debs* et al. nor *Ruskewicz* et al. remedy this deficiency of *Huland* et al. Applicants submit that independent claims 15 and 22, along with their dependent claims 16-21 and 23, are patentable over *Huland* et al., *Debs* et al. and *Ruskewicz* et al., alone or in any combination, at least for the foregoing reasons. Withdrawal of the rejection is therefore respectfully requested.

35 U.S.C. § 112, first paragraph

Claim 15 stands rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner contends that, although the specification describes stabilizing agents such as sugar, alcohol, and amino acids, it does not describe the combination of these agents. Applicants respectfully traverse this rejection.

The test for sufficiency of support in an application is whether the disclosure at the time of filing "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." MPEP 2163.02 (quoting *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983). The description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption." MPEP 2163 III. A. It is the Examiner who bears "the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims." MPEP 2163. III. A. Furthermore, the Examiner is reminded that "[m]ere rephrasing of a passage does not constitute new matter." MPEP 2163.07 I.

Applicants submit that in light of the foregoing guidelines, the disclosure clearly conveys to the artisan that Applicants were in full possession of the subject matter of claim 15. Claim 15 originally recited an aqueous gamma-IFN solution "containing a stabilizing agent." The term "containing" is an open-ended term that is comparable to the term "comprising." MPEP 2163 II. A. 1. The disclosure specifically recites that each of sugar, alcohol, or amino acid are suitable for use as stabilizing agents in the present invention. (page 7, lines 26-28). Applicants submit that this original claim language, therefore, clearly includes within its scope an aqueous gamma-IFN solution comprising a combination of sugar, alcohol, or amino acid as stabilizing agents.

Claim 15 as amended in the Applicants' previous Response recites aqueous gamma-IFN solution "comprising a stabilizing agent consisting of sugar, alcohol, amino acid, or a

combination thereof." Applicants respectfully submit that the phrase "a combination thereof" is merely a rephrasing of the original claim language, which also included within its scope a combination of stabilizing agents. The phrase "a combination thereof" does not alter the meaning of the claim, and is therefore proper as is indicated by the MPEP.

Furthermore, as stated above, the disclosure specifically recites that **each** of sugar, alcohol, or amino acid are suitable for use as stabilizing agents in the present invention. Given this disclosure, it would reasonably be expected that a combination of these compounds would also be effective as a stabilizing agent. Consequently, on reading the specification it is readily understood that Applicants were in possession of aerosol compositions comprising a stabilizing agent that is a combination of sugar, alcohol, or amino acid at the time of the invention. Applicants submit that the Examiner has not articulated any reason why the disclosure that sugars, amino acids, and alcohols are suitable stabilizing agents would not immediately and reasonably convey that a combination of these agents would also be suitable, and that Applicants therefore were in possession of this embodiment. Therefore, the Examiner has not met the initial burden of demonstrating a lack of written support. Applicants submit that the specification provides ample support for claim 15 as written, at least for the foregoing reasons. Withdrawal of the rejection is therefore respectfully requested.

Summary

Applicants submit that the claims are in condition for allowance and notification to that effect is earnestly solicited. The Examiner is invited to contact Applicants' representative if prosecution may be assisted thereby.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332.5300

Date: 2/17/04

Garen Gotfredson

Garen J. Gotfredson
Reg. No. 44,722
GJG